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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/063,699	05/08/2002	Dan L. Eaton	P3230R1C001-168	9949

30313 7590 12/16/2004

KNOBBE, MARTENS, OLSON & BEAR, LLP
2040 MAIN STREET
IRVINE, CA 92614

EXAMINER	
DUFFY, PATRICIA ANN	
ART UNIT	**PAPER NUMBER**
1645	

DATE MAILED: 12/16/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/063,699	EATON ET AL.	
	Examiner	Art Unit	
	Patricia A. Duffy	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 October 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8,11-14 and 16-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,11-14 and 16-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The preliminary amendment 9-10-02 has been entered into the record.

The response, amendment, information disclosure statement, Exhibits 1-8 filed October 5, 2004 have been entered into the record. It is noted that Exhibits I and II are declarations pursuant to 37 C.F.R § 1.132 executed by J. Christopher Grimaldi. Exhibits III and VII are declarations pursuant to 37 C.F.R § 1.132 executed by Paul Polakis, PhD. and Avi Ashkenazi Ph.D. respectively. Claims 1-8, 11-14 and 16-20 are pending and under examination. Claims 9-10 and 15 having been cancelled.

The text of Title 35 of the US Code not cited herein, is of record in the first office action on the merits mailed 7-2-04.

Correction of Inventorship

Pursuant to the request under 37 C.F.R. §1.48(b) signed by a party set forth in §1.33(b) and the filing of the processing fee set forth in § 1.17(i), the following individuals have been removed as inventors: Dan L. Eaton, Ellen Filvaroff, Mary E. Gerritsen and Colin K. Watanabe.

Rejections Withdrawn

The objection to the title is withdrawn in view of Applicants' amendment.

The objection to the specification as lacking a paper copy of the sequence listing as required by 37 C.F.R. § 1.821(c) is withdrawn in view of the amendment to the specification.

The objection to the specification for the use of the trademarks TWEEN™, PLURONICS™ AND LIFESEQ™ is withdrawn in view of the amendments to the specification.

The rejection of the claims under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which

applicant regards as the invention is withdrawn in view of Applicants' amendments to the claims.

Rejections Maintained

Priority

Applicants argue that the nucleic acids have credible, specific and substantial utility and that they are entitled to the priority date of 6-10-98 of provisional document 60/099,812. The provisional document does not provide written description of the claims as now set forth for reasons made of record. The provisional document fails to establish utility/enablement and written description for the now claimed nucleic acids, vectors and host cells. Description of the nucleic acid in the provisional application does not provide compliance with 35 USC § 120 for reasons set forth in the previous office action of record and reasons set forth herein. Applicants are not granted priority for the provisional document 60/099,812.

Applicants argue that the data in Example 18 (tumor versus Normal Differential Tissue Expression Distribution), relied on in part for the utility of the claimed nucleic acids, were first disclosed in PCT Application PCT/US00/23328 filed 8-24-00 on page 93, line 3, through page 96, line 35. This is not persuasive, the priority document does not comply with 35 USC § 120, written description, utility and enablement for reasons set forth in the previous office action of record and reasons set forth herein.

The priority date for prior art purposes is the instant filing date of 5-8-02.

Information Disclosure Statement

The information disclosure statement filed 10-5-04 has now been considered with respect to the individual sequences set forth in the Blast Alignment, an initialed copy is enclosed.

Rejections Maintained

Claims 1-8, 11-14 and 16-20 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific, substantial and credible asserted utility or a well established utility is maintained for reasons made of record in the office action mailed 7-12-04 and reasons made of record herein.

Applicants rely upon the utility that the nucleic acid is more highly expressed in *normal* skin as compared to melanoma. Neither the nucleic acid nor the encoded protein have a substantial utility or well-established utility. The utility for the encoded protein is of relevance for the claims as drawn to the nucleic acid encoding a protein. With respect to the nucleic acid of SEQ ID NO:51 and hybridizing variants thereof, it is asserted that the PRO polynucleotide can be used in tumor/cancer diagnostics or therapeutics. The specification also discloses that PRO1411 tested positive in a single analysis to detect overexpression of PRO polynucleotides in tissues (see Example 18 of specification). The specification teaches that the nucleic acid of SEQ ID NO:51 was "more highly expressed" in normal tissues, the corollary being "under-expressed" in melanoma. This information does not provide a specific and substantial or well established utility for PRO polynucleic acids/encoding polynucleotides, polypeptides or antibodies. The data presented in the assay are preliminary at best, and cannot be evaluated or repeated independently by the skilled artisan. The specification does not set forth the number of independent samples tested, the levels of the nucleic acid or protein in the samples such that the "higher" levels in normal tissue as compared to levels in melanoma was determined to be statistically significant. The specification does not set forth the conditions and the probes used to determine the "levels" of SEQ ID NO:51 in the sample tested and the skilled artisan would not know under what conditions and using what probes that a difference in expression could be detected. It is not clear, for example, if under/overexpression was detected in 1/10 or 10/10 independent samples tested. There is no guidance in the specification of how to use a finding that has not been demonstrated to

be reproducible and statistically significant with multiple independent samples. No levels (relative or absolute) are disclosed in the specification as originally filed. The disclosed information is too sparse to allow either SEQ ID NO:51, the encoding polynucleotide for the polypeptide of SEQ ID NO:52 or variants thereof to be used as a diagnostic marker for melanoma. Because it is not known in the art, and the specification does not teach if the nucleic acid is involved in causing/suppressing the melanoma, the skilled artisan could not use the nucleic acid or encoded protein therapeutically as a target for the treatment of cancer. The nucleic acid encoding the polypeptide has no utility because (1) the nucleic acid of SEQ ID NO:51 per se has no utility and (2) the encoded protein has no utility (i.e. as it relates to the embodiments claiming a nucleic acid encoding a polypeptide). The actual biological activity of the encoded polypeptide is not set forth in the art or the specification. Applicants generally teach that the hybridization signal of a probe from a normal tissue sample is greater or less than hybridization from a disease tissue sample, the gene or genes under- or over-expressed in the disease tissue are identified. The implication of this result is that an under-/over-expressed protein in a disease tissue is useful not only as a diagnostic marker for the presence of the disease condition, but also as a therapeutic target for treatment of the disease condition. It is specifically noted that Applicants have not measured expression of the polypeptide *per se*, nor have they demonstrated increased mRNA expression as compared to an appropriately matched tissue control and show that the difference is statistically relevant for melanoma samples as compared to normal skin. Further, the skilled artisan would not believe the assertion that the level of DNA is correlated with the level of mRNA and corresponding level of encoded polypeptide for reasons made of record herein. The teachings of the specification are limited to an apparently single test using undisclosed probes/primers and conditions and fails to establish qualitative or quantitative measures for mRNA or protein. The specification fails to establish that the expression pattern is statistically significant with multiple independent samples of different patient samples having the same cancer type as

compared to normal tissues. Clearly, further research would be required of the skilled artisan to establish whether and how a nucleic acid/probe/mRNA or encoded polypeptide used could be used as diagnostic markers or therapeutic targets. Such further experimentation indicates that the asserted utility is not in currently available form.

Applicants rely upon the utility that the nucleic acid is more highly expressed in normal skin as compared to melanoma (Example 18, of the specification).

Applicants' arguments have been carefully considered but are not persuasive. Applicants argue that the requirement for a substantial utility defines a "real world use" and cite *Brenner v Manson*, 383 US 519,514(1996) already of record. Applicants argue that MPEP 2107.01 that states that office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulation to mean that products or services based on the claimed invention must be "currently" available to the public. This is not persuasive, the rejection set forth did not require "current public availability", but a specific and substantial utility for the now claimed invention. Applicants argue that any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient, at least with regard to defining a "substantial utility". This is not persuasive, the relied upon utility (decrease nucleic acid/mRNA or protein expression in melanoma as compared to normal skin) specifically requires or constitutes carrying out further research to identify or reasonably confirm a "real world" context of use and as such is therefore not a "substantial utility" (see MPEP 2107.01(1)). Applicants argue that the USPTO must establish that it is more likely than not that one of skill the art would doubt the truth of the statement of utility, namely that the nucleic acid or gene encoding PRO1411 is differentially expressed in certain cancers compared to normal tissue and useful as a diagnostic tool. The argument has been fully considered, but is not persuasive. Utility requires that the skilled artisan be able to use the claimed invention. The specification does not provide a substantial or a well-established use for the foregoing reasons. Applicants have provided a single analysis

of a nucleic acid without any relative range or detection for basing a utility of over-/under-expression for the claimed nucleic acid or protein(s). There is no guidance on how to use this information. No levels (relative or absolute) are disclosed. Applicants argue that if the gene is differentially expressed in cancer versus non-cancer tissue, then its mRNA and encoded polypeptide are useful as diagnostics. This argument is pertinent to the instant claims because of the limitation added wherein said isolated nucleic acid is more highly expressed in normal skin as compared to melanoma or wherein the nucleic acid encodes a polypeptide that is more highly expressed in normal skin as compared to melanoma. The argument has been fully considered, but is not persuasive for reasons made of record herein. Further, if one cannot use the encoding nucleic acid as a diagnostic tool for tumors, then one cannot use the encoded polypeptide either. There is no data regarding protein expression in melanoma and normal skin tissue in the specification and Applicants are attempting to rely upon a correlation of increased DNA to increased mRNA levels of SEQ ID NO:51 with increased protein levels (SEQ ID NO:52; PRO1411). The art clearly establishes that DNA copy number, mRNA levels and protein levels are not inexorably related, in that an increase/decrease in one necessarily leads to an increase in all of them. Transcription levels (mRNA) do not correlate with polypeptide levels and Applicants have not provided any specific role for the lack of the claimed polypeptide in cancer or identified its biological function in suppression of cancer. Haynes et al. (1998, Electrophoresis 19:1862-1871), who studied more than 80 proteins relatively homogeneous in half-life and expression level, and found no strong correlation between protein and transcript level. For some genes, equivalent mRNA levels translated into protein abundances that varied more than 50-fold. Haynes et al. concluded that the protein levels cannot be accurately predicted from the level of the corresponding mRNA transcript (p. 1863, second paragraph, and Figure 1). Further, the concept that transcription levels do not correlate with protein levels was so well known to the art that it was presented in a text book Lewin, Genes VI (1997) Chapter 29, pages 847-848 which specifically teaches "...

production of RNA cannot be inevitably be equated with production of protein...." (page 487, column 2, last paragraph). This concept reconfirmed by a variety of studies such as that evidenced by Gokman-Polar et al (Cancer Research 61:1375-1381, 2001) that indicates the absence of any necessary correlation between increased mRNA levels and increased protein levels. Gokman-Polar et al that teach "Quantitative reverse transcription-PCR analysis revealed that the PKC mRNA levels do not directly correlate with PKC protein levels, indicating that PKC isoenzyme expression is likely regulated at the posttranscriptional/translational level" (see abstract). Gokman-Polar et al show in Figure 6-7 that there is no increasing mRNA expression for any of the isoenzymes, while the protein is significantly overexpressed as shown by Figure 4-5. Further, Pennica et al (PNAS, 95:14717-22, 1998) establishes that there is a lack of correlation between gene amplification and protein expression of the WISP protein and this teaching in combination with Haynes et al indicates that there is no significant correlation between nucleic acid level and translation indicates that the asserted correlation between each gene, mRNA and corresponding protein in tumors and normal tissue is unpredictable and that such was well known to the skilled artisan at the time of filing. Applicants have presented no showing that the amount of both the mRNA(gene) and protein are statistically increased in normal cells as compared to melanoma PRO1411. Hu et al. (2003, Journal of Proteome Research 2:405-412) analyzed 2286 genes that showed a greater than 1-fold difference in mean expression level between breast cancer samples and normal samples in a microarray (p. 408, middle of right column). Hu et al. discovered that, for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a known role in the disease. However, among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease (see discussion section). This specification does not teach the expression level of the claimed mRNA or protein, nor is it demonstrated scientifically significant and is therefore at best a

preliminary observation that requires substantive experimentation to ascertain the veracity thereof across multiple independent samples to ascertain if the preliminary observation is statistically significant or relevant to any role in indicated tumors/cancer. Therefore, the art indicates that it is not the norm that increased/decreased gene transcription results in increased/decreased polypeptide levels and the asserted utility of the PRO1411 polypeptides as diagnostic markers and therapeutic targets are simply starting points for further research and investigation into potential practical uses of the claimed polynucleotides and polypeptides. The need for further research to reasonably identify or confirm a utility is not "substantial" because it does not identify a "real world" utility (MPEP 2107.01(1)). Even if the nucleic acid has a utility as a melanoma marker (a point that the examiner does not concede) , the nucleic acid encoding the protein does not have utility because the protein has no utility and it is not known what the protein does or if the level of the PRO1411 protein in melanoma corresponds to transcript level (i.e. if an decreased amount of transcript corresponds to an decreased amount of expressed protein or vice versa) for reasons made of record. It does not necessarily follow that an decrease in transcript levels results in a corresponding decrease in protein expression, such that the polypeptide would be useful diagnostically or as a target for cancer drug development. The cited references establish that one skilled in the art would not associate DNA copy number, mRNA and protein levels and necessarily reflecting each other. Applicants argue that the utility is credible. It is noted that credibility for the asserted utility for the PRO1411 polypeptides as claimed has not be assessed because the relied upon utility is not deemed substantial or well established for reasons of record.

The utility now asserted and relied upon for the claimed polypeptide is more highly expressed in normal tissues respect to corresponding melanoma and that this differential expression provides for a specific, substantial, and credible utility. This is not persuasive, Applicants have not shown that the polypeptide as shown in SEQ ID NO:52 or any claimed variant or fragment thereof is under-expressed as compared to normal tissue samples.

Applicants argue that as provided in Example 18 of the application, the nucleic acid of SEQ ID NO:51 is under-expressed in melanoma relative to normal skin and that this differential expression provides a specific, substantial and credible utility for the now claimed polypeptide. Applicants further rely upon the Grimaldi declarations submitted as Exhibits 1 and 2 to post facto attempt to establish that the nucleic acid in melanoma is significantly lower than that in normal skin. These declarations are not persuasive for the following reasons. As to the first declaration of Dr. Grimaldi (Exhibit 1), Declarant Grimaldi merely reiterates the assertion in the specification that since the RNA levels are different then "this indicates that the gene and its corresponding polypeptide and antibodies are useful for diagnostic purposes to screen samples to differentiate between normal and tumor." This is not persuasive, the assertion relies upon a tight correlation of RNA production with protein expression. The art, as set forth *supra*, clearly recognizes that RNA production does not correlate with protein expression. Declarant also explains how the assay of Example 18 was done and the scoring procedure used. Declarant asserts at paragraph 6, that the expression levels in the tumor and normal vary by at least two fold based on a visual quantification using ethidium bromide staining of PCR products on agarose gels. This is not persuasive, visual detection is highly subjective and was graded as + or – or +/- and not is quantitative. Applicants have not set forth the evidentiary basis for their assumption that a visual difference relates to an at least 2-fold difference in cDNA or 2 fold difference in protein. The statistical relevance of such a difference across multiple independent samples is not addressed by Declarant. Applicants have provided no objective evidence that supports this assertion of qualitative and quantitative results or statistical relevance thereof. With respect to the pooled samples, Declarant says, "That is, the detection of variations in gene expression is likely to represent a more generally relevant condition when pooled samples from normal tissues are compared with pooled samples from tumors in the same tissue type," [paragraph 5] without knowing the range of variation there is insufficient guidance for a diagnostic assay. If a clinician took a skin tissue

sample from a patient with suspected melanoma, what is the likelihood that when compared with normal tissue, the level of nucleic acid of SEQ ID NO:51 from the patient would be lower? How many samples would be needed? What sensitivity would be needed? Would the normal tissue have to be a pooled sample or could it be from a single individual? Further, this appears to be the opinion of Declarant because it is not supported by objective evidence set forth before the examiner. While the 6th paragraph of the first Grimaldi Declaration says that the detection technique used in the specification makes it "reasonable to assume that any detectable differences seen between two samples will represent at least a two-fold difference in cDNA," that statement still does not answer the questions raised above and does not place a specific and substantial use of the nucleic acid or polypeptide encoded thereby in the skilled artisan's hand. The statement that the relative difference in expression is what is important is generally true, but without more specifics about necessary sample size, expression level range for normal and tumor tissues that can used, and other questions, the specification has not provided the invention in a form readily usable by the skilled such that significant further experimentation was unnecessary. The courts have held that the disclosure is insufficient when testing is necessary to determine the actual use or possible lack of use *(In re Kirk and Petrow* (CCPA) 151 USPQ 48) .

The second declaration by Dr. Grimaldi (Exhibit 2) has been fully considered but is not deemed persuasive. Applicants argue the second declaration of Dr. Grimaldi (Exhibit 2) that states that "in the vast majority of cases, when a gene is over-expressed , as evidenced by an increased production of mRNA, the gene product or polypeptide will also be over-expressed and that the detection of increased/decreased mRNA expression is expected to result in increased/decreased polypeptide expression. At paragraph 4, Declarant discusses mutations of Her2/Neu, and chromosomal translocations that are known to be associated with cancer, and states the "When the chromosomal aberration results in the aberrant expression of mRNA and the corresponding gene product (the

polypeptide) , as it does in the aforementioned cases, the gene product is a promising target for cancer therapy, for example, by the therapeutic antibody approach.". This argument has been fully considered but is not persuasive because it evinces that the instant specification provides a mere invention to experiment, and not a readily available utility. Further, there is no cancer antibody therapeutic in the art that relies upon a polypeptide that is under expressed in cancer. The therapeutic antibodies of the art rely upon statistically relevant increased polypeptide expression or unique polypeptide expression. Thus, there is no basis for asserting that therapeutic antibodies would be useful in any scenario where the protein is under-expressed in the tumor. The PRO1411 gene, unlike Her2/Neu, has not been associated with tumor formation or the development of cancer, nor has it been shown to be predictive of such. Similarly, unlike t(5;14), no translocation of PRO1411 is known or established to occur. All that the specification demonstrates that the PRO1411 mRNA "more highly expressed" in normal skin as compared to melanoma without any statistical analysis, the relevance of a single point is unreliable and unpredictable. No mutation or translocation of PRO1411 has been associated with melanoma. It is not known what whether PRO1411 polypeptide is expressed in melanoma and normal skin and what the relative levels of expression are. In the absence of any of the above information, all that the specification does is present evidence that the DNA encoding PRO1411 is "more highly expressed" a normal sample, and invite the skilled artisan to determine the rest of the story (i.e. biological relevance, independent samples, statistical significance and correlation with protein expression). Such is insufficient to meet the requirements of 35 U.S.C. § 101 for the instantly claimed protein. At paragraph 5, Declarant argues that increased mRNA expression is expected to be associated with increased protein production. This argument has been fully considered but is not deemed persuasive because (a) this appears to be Declarant's opinion, and is not supported by fact or evidence (b) there has been no distinction on the record in general or in the specification as filed between total nucleic acid, which includes chromosomal DNA and

mRNA. One cannot determine for the data in the specification whether the observed "more highly expressed" is due to mutation, copy number differences or transcription rates. It remains that there is no information on the record as to whether the claimed protein is expressed at all in normal tissue, cancerous or otherwise and whether the nucleic acid expression levels correlate with the actual protein levels. It remains that, as evidenced by Pennica et al, Haynes et al, Gokman-Polar et al and Lewin, the issue is simply not predictable, and the specification presents a mere invitation to experiment to determine the relevance of "more highly expressed" in relation to both the nucleic acid and the protein. This is further borne out by Declarant's paragraph 6, which proposes further experimentation, should Applicants assertions be erroneous and there is no direct correlation between gene expression and protein expression.

Applicants also present a declaration by Dr. Polakis and referenced in the response as Exhibit 3. In the declaration, Dr. Polakis states that the primary focus of the Tumor Antigen Project was to identify tumor makers useful as targets for cancer diagnostics and therapeutics. Dr. Polakis states that approximately 200 gene transcripts were identified that are present in human tumor cells at significantly higher levels than in corresponding normal human cells. Dr. Polakis states that antibodies to approximately 30 of the tumor antigen polypeptides have been developed and used to show that approximately 80% of the samples show correlation between increased mRNA levels and changes in polypeptide levels. Dr. Polakis states that it remains a central dogma that in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded polypeptide. Dr. Polakis characterizes reports of instances where such a correlation does not exist, as exceptions to the rule. This has been fully considered but is not found to be persuasive. The declaration does not provide data such that the examiner can independently draw conclusions, or provide any objective evidence with respect to the instantly claimed statistical relevance or levels of nucleic acids, nucleic acid encoding polypeptides or polypeptides. Only, Dr. Polakis' conclusions are provided in the declaration.

There is no evidentiary support to Dr. Polakis' statement that it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded polypeptide and the examiner has presented evidence that one of skill in the art would not believe this to be true. Further, while the declaration may allege (no evidence is presented) that there is a correlation between mRNA expression and protein over-expression in some cases, Applicants have presented no objective evidence that the PRO1411 polypeptide is under-expressed as asserted, relative to normal cells and that the difference is statistically relevant with respect to the nucleic acids and polypeptides. It is noted that the literature cautions researchers from drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue. For example, Hu et al (Journal of Proteome Research 2:405-412, 2002) analyzed 2286 genes that showed a greater than 1-fold difference in mean expression level between breast cancer samples and normal samples in a microarray (page 408, middle of right column). Hu et al discovered that, for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a known role in the disease. However, among genes with a 10-fold change in expression level, there was a strong and significant correlation between expression level and a published role in the disease (see discussion section).

Applicants argue additional references to support the position that changes in DNA gene levels correlated with levels of mRNA expression and levels of protein expression (Orntoft et al, Hyman et al and Pollack et al; Exhibits 4-6). Applicants characterize Orntoft et al as teaching in general (18 of 23 cases) chromosomal areas with more than 2-fold gain of DNA showed a corresponding increase in mRNA transcripts. Applicants characterize Hyman et al a providing evidence of a prominent global influence of copy number changes on gene expression levels. Applicants characterize Pollack et al as teaching that 62% of highly amplified genes show moderately or highly elevated expression and that on average, a 2-fold change in DNA copy number is associated with a

1.5-fold change in mRNA levels. The arguments related to these references have been fully considered but are not persuasive. Orntoft et al appear to have looked at increased DNA content over large regions of chromosomes and comparing that to mRNA and polypeptide levels from the chromosomal region (see for example page 44, column 1, last paragraph). Their approach to investigating gene copy number was term CGH. Orntoft et al do not appear to look at gene amplification, mRNA levels and polypeptide levels from a single gene at a time. The instant specification reports data regarding mRNA levels, from an unknown number of genes, which may or may not be in a chromosomal region that is highly amplified. Orntoft et al concentrated on regions of chromosome with strong gains of chromosomal material containing clusters of genes (page 40). This analysis was not done for PRO1411 genes in the instant specification. That is, it is not clear whether or not PRO1411 is in a gene cluster in a region of the chromosome that is highly amplified. Therefore, the relevance of Orntoft et al is not clear. Hyman et al used the same CGH approach in their research. Less than half (44%) of the highly amplified genes showed mRNA overexpression (see abstract). Therefore, it is not "more likely than not" that amplified DNA=amplified mRNA=amplified polypeptides. Polypeptide levels were not investigated and therefore do not speak to the relationship between mRNA levels and polypeptide levels, which one of the issues here as it relates to a nucleic acid encoding a polypeptide. Therefore, the relevance of Hyman et al as it relates to the issue of correspondence of DNA levels and mRNA with levels of polypeptide expression is not "more likely than not" and Hyman et al does not support utility of the claimed polypeptides. Pollack et al also used CGH technology, concentration in large chromosome regions showing high amplification (page 12,965). Pollack et al also did not investigate polypeptide levels and therefore does not speak to the issue of the correlation of levels of mRNA and encoded polypeptide. Pollack et al also noted contradictory results found by another research group, noting that , "Alternatively, the contrasting findings for amplified genes may represent real biological differences between breast and metastatic colon

tumors; resolution of this issue will require further studies" (page 12,968 end of first paragraph). This leads again to the issue of unpredictability. Therefore, Pollack et al also does not support the asserted utility of the claimed invention. Importantly, none of the later papers reported that the research was relevant to identifying probes that can be used as cancer diagnostics. The three papers state that the research was relevant to the development of potential cancer therapeutics, but also clearly imply that much further research was needed before such therapeutics were in readily available form. Accordingly, the specification's assertions that the claimed PRO1411 polypeptides have utility in the fields of cancer diagnostics and cancer therapeutics are not substantial.

Applicants argue that even assuming *arguendo* that there is no correlation between gene expression and protein expression for PRO1411, a polypeptide that is underexpressed or overexpressed in some undefined cancer is still useful and present Exhibit 7, a declaration filed by Dr. Ashkenazi. Dr. Ashkenazi declares that the absence of gene product over-expression still provides significant information for cancer diagnosis because it enables more accurate tumor classification and hence better determination of suitable therapy. This is not persuasive, there is no evidence that clinicians use information about a gene product NOT being overexpressed as a basis for deciding to not treat a patient with an agent that targets that gene product. The specification does not teach how the PRO1411 relates to tumor classification using any clinically relevant standards (i.e. invasive potential, drug resistance, primary or secondary tumor) upon which oncologists (i.e. the skilled artisan in cancer treatment) rely to make therapeutic decisions. Neither, the specification nor the art indicates or contemplates how the claimed PRO1411 polypeptide under- or over-expression fits into the alleged tumor classification or to any tumor classification for that matter. Applicants allege that the information of PRO1411 expression or over-expression leads to better determination of a suitable therapy. This is not persuasive, the biological role of PRO1411 in cancer, if any, is not set forth in the specification and it is not clear how the specification leads a clinical to a "better

determination of suitable therapy" as asserted by Applicants. This is a hypothetical utility that is not disclosed in the specification. The specification does not disclose the function of PRO1411 as it relates to cancer prevention/promotion and therefore it is not readily apparent to the skilled artisan how to apply any level determination of any disclosed nucleic acid or polypeptide with any of the plethora of cancer therapies available to the clinician oncologist (i.e. the skilled artisan in cancer therapy). The function (estrogen receptor) and relationship of Her/Neu2 is clearly established in breast cancer. This function and relationship is not established in the specification for PRO1411 as it relates to melanoma or normal skin cells or any other cell in the art. As such, the polypeptide does not have a well established or substantial utility for the claimed polypeptides.

Applicants argue that the utility of the PRO1411 polypeptide is further supported by the teachings in the article by Hanna et al, submitted as Exhibit 8 that show that for Her-2, to diagnose breast cancer both the gene product presence as well as amplification of the gene itself provides for the most complete information. This argument has been considered but is not persuasive. Hanna et al say that these tests are used more or less independently, with the protein test used first, followed by the gene test if the protein test is negative (column 2, third full paragraph). The protein test is only necessary to determine the appropriateness of antibody therapy. Also, it is stated in the same paragraph that "in general, FISH[gene] and IHC[protein] results correlate well for Her-2. However, subsets of breast tumors are found that demonstrate discordant results, i.e. protein overexpression without gene amplification or lack of protein overexpression with gene amplification. The clinical significance of such results is unclear." Therefore, the issues of Her-2 and breast cancer cannot be generalized to any gene expressed in any tumor. As such, Hanna et al is not dispositive of the central issue herein, the correlation of gene levels, mRNA levels and protein levels and predictability thereof.

Since the claims are directed to the nucleic acid encoding a PRO1411 polypeptide, it was imperative to find evidence in the relevant scientific literate whether or not a small

increase in DNA copy number or mRNA levels would be considered by the skilled artisan to be predictive of increased mRNA and subsequence encoded protein levels. Pennica et al was cited as evidence showing a lack of correlation between gene (DNA) amplification and elevated mRNA levels. Further, Konopka et al (PNAS, 83:4049-52, 1986) states that "Protein expression is not related to amplification of the *abl* gene but to variation in the level of bcr-abl mRNA production from a single Ph1 template" (see abstract). Konopka et al also provide evidence that showing lack of correlation between gene amplification and increased polypeptide level. Gokman-Polar et al and Lewin were cited to teach the lack of correlation between mRNA levels and protein levels was so well established in the art it was cited in a textbook and experimentally exemplified by Gokman-Polar et al. Finally, it is noted that the literature of record cautions researchers from drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissues. Haynes et al was cited to provide evidence that polypeptides levels cannot be accurately predicted from mRNA levels, and that variances as much as 40-fold or even 50-fold were not uncommon (page 1863). Given even the asserted "visible 2-fold increase in mRNA" (Declaration Dr. Grimaldi as Exhibit 1), and in the evidence presented by Haynes et al, Gokman-Polar et al and Lewin, it is clear that one skilled in the art would not assume that a small increase/decrease in DNA or mRNA would correlate with corresponding changes in polypeptide levels or role in disease. Given the evidence provided by Haynes, Pennica et al and Konopka et al it was clear that one skilled in the art would not assume that a small increase in gene copy number would correlate with significantly increased mRNA levels or encoded polypeptide levels. In view of the totality of the evidence of record, one skilled in the art would not assume that gene number or gene expression necessarily parallels or is predictive of protein expression and would have to perform further experimentation to verify or rule it out. As such, this further experimentation indicates that the asserted utility is not "substantial".

The rejection is maintained for reasons made of record.

Claim 1-8, 11-14 and 16-20 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific, substantial and credible asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Claims 1, 2, 3, 4, 5, 14 and 16-20 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention is maintained for reasons made of record for claims 1-6, 8-10 and 14-20 in the first office action on the merits mailed 7-12-04.

Applicants' arguments have been carefully considered but are not persuasive. Applicants argue that the amendment of the claims to recite the limitation of wherein the isolated nucleic acid is more highly expressed in normal skin cells to relative to melanoma or in the alternative recite wherein said isolated nucleic acid encodes a polypeptide that is more highly expressed in normal skin tissue relative to melanoma, provides for sufficient distinguishing identifying characteristics of the genus. Neither the specification nor the art provides for a known or established correlation of structure with the recited limitation. This is not persuasive, the limitation does not impart specific structural requirements for possession of nucleic acids as set forth. The specification does not provide complete or partial structure of a representative number of nucleic acids that meet the now recited limitation. The skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description of a genus is more

than a mere statement that it is part of the invention and reference to a potential methods of isolating it. The compound itself is required. The specification teaches a single nucleic acid SEQ ID NO:51 that allegedly meets the limitation of "more highly expressed in normal tissues (skin) relative to diseased tissue (melanoma)". The specification does not teach that the polypeptide *per se* is more highly expressed. The specification does not teach variants of either the nucleic acid or polypeptide that have these properties as claimed. There are no other nucleic acids or polypeptides in the specification as originally filed that fall within the claimed genus. As such, the skilled artisan would not be able to readily envision the claimed genus.

Applicants argue that with respect to hybridization conditions that according to Example 9 of the Written Description Guideline Training Materials provides that one would not expect substantial variation among the species encompassed. This is not persuasive, the hybridization is not to SEQ ID NO:51 but encoding variants thereof, which can be up to 30% different than SEQ ID NO:51. Further, it is specifically noted in Example 9 of the Written Description Guideline Training Materials that absent some isolation of nucleic acid with the asserted function using the hybridization conditions, the recitation of mere hybridization conditions does not provide for possession and written description of "hybridizing nucleic acids". Unlike Example 9 of the Training Guidelines, this specification fails to provide written description of a single nucleic acid that was isolated by hybridization to either SEQ ID NO:51 or variants of the nucleic acid encoding the polypeptide of SEQ ID NO:52. Therefore, the skilled artisan would clearly recognize that Applicants were not in possession of the claimed subject matter. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written

description for the broad class. The specification provided only the bovine sequence. Similarly, the specification only teaches the nucleic acid of SEQ ID NO:51 that encodes the polypeptide of SEQ ID NO:52. As such, the single disclosed nucleic acid is not an adequate written description of hybridizing variants, and percent identity variants of SEQ ID NO:51 *per se* or nucleic acids encoding protein variants. Finally, University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that:

> ...To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." *Lockwood v. American Airlines, Inc.* , 107 F.3d 1525, 1572, 41 USPQ2d 1961, 1966 (1997); *In re Gosteli* , 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood* , 107 F.3d at 1572, 41 USPQ2d at 1966.
>
> An adequate written description of a DNA, such as the cDNA of the recombinant plasmids and microorganisms of the '525 patent, "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention. *Fiers v. Revel* , 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). Accordingly, "an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." Id. at 1170, 25 USPQ2d at 1606.

The specification fails to teach a single variant of a polypeptide sequence of SEQ ID NO:52 and it is noted that the claimed polynucleotides do not exist as an invention independent of their function in encoding a putative protein. The actual structure or other relevant identifying characteristics of each nucleic acid that encodes a variant protein having the claimed properties of the underexpressed protein herein can only be determined empirically by actually making every nucleic acid that encodes the recited variability (i.e. the substitutions, insertions or deletions as compared to SEQ ID NO:51) and testing each to determine whether it encodes a protein having the particularly disclosed properties of the protein of SEQ ID NO:52. As noted in the Guidelines at Section I.A.(2):

> There is an inverse correlation between the level of predictability in the art and the amount of disclosure necessary to satisfy the written description requirement. For example, if there is a well-established correlation between structure and function in the art, one skilled in the art will be able to reasonable predict the complete structure of the claimed invention from its function.

The specification proposes the converse, yet still does not meet the requirements for an adequate written description of the claimed invention. The specification proposes that the skilled artisan is to modify a known nucleic acid sequence encoding a known protein sequence and that modification would still describe applicants' invention as a protein "underexpressed in melanoma". The protein disclosed as SEQ ID NO:52, has no disclosed or described biological activity. The limitation of expression claimed herein is determined by the structural nucleotide sequence that encodes it. There must be some nexus between the structure of a nucleotide sequence and the structure of the protein encoded, and the function of that encoded protein. However, function can not be predicted from the modification of the structure of the gene sequence or in this case the nucleotide sequence encoding the protein. The specification has not shown that, by modifying a reference

sequence encoding a reference polypeptide as claimed, will automatically predict the production of a protein having the limitation as claimed. While it is true that, due to the nature of codon degeneracy, applicant may take a reference sequence and modify that sequence to be a different nucleic acid sequence, yet still have that nucleic acid encode the same protein. The specification fails to teach the structure or relevant identifying characteristics of a representative number of species of a representative number of polynucleotides encoding a representative number proteins having the same property, sufficient to allow one skilled in the art to determine that the inventor had possession of the invention as claimed. The specification fails to provide a representative number of protein or nucleic acid variants to indicate that applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the single disclosed nucleic acid species of SEQ ID NO:51. Applicants' proposed insertions, deletions or substitutions to that nucleic acid sequence do not predict a protein having all the claimed limitations of the encoded protein as disclosed. Therefore, such undisclosed and unidentified nucleic acids that result from these, insertions, deletions or substitutions encompasses by the recited hybridization conditions or percent variation are not described. These altered nucleic acids would encode a polypeptide that would vary from the disclosed protein of SEQ ID NO:52 in some unknown or unpredictable manner. *Amgen Inc. v. Chugai Pharmaceutical Co. Inc.* 18 USPQ2d 1016, 1026 (CAFC 1991) addressed a similar issue of enablement and undue experimentation for analogs of erythropoietin (EPO) gene broadly claimed and narrowly disclosed. In that instance, it was found:

> that over 3,600 different EPO analogs can be made by substituting at only a single amino acid position, and over a million different analogs can be made by substitution three amino acids. The patent indicates that it embraces means for preparation of "numerous" polypeptide analogs of EPO. Thus, the number of claimed DNA

sequences encoding sequences that can produce EPO-like product is potentially enormous.

Further, at page 1027, the CAFC found that:

> it is not necessary that a patent applicant test all the embodiments of his invention, ... what is necessary is that he provide a disclosure sufficient to enable one skilled in the art to carry out the invention commensurate with the scope of the claims. For DNA sequences, this means disclosing how to make and use enough sequence to justify a grant of the claims sought. Amgen has not done that here. In addition, it is not necessary that a court review all of the *Wands* factors to find a disclosure enabling. They are not illustrative, not mandatory. What is relevant depends on the facts, and the facts here are that Amgen has not enabled preparation of DNA sequences to support its all-encompassing claims... Here, however, despite extensive statements in the specification concerning all the analogs of the EPO gene that can be made, there is little enabling disclosure of particular analogs and how to make them. Details for preparing only a few EPO analogs genes are disclosed. Amgen argue that this is sufficient to support its claims; we disagree. This "disclosure" might well justify a generic claim encompassing these and similar analogs, but it represents inadequate support for Amgen's desire to claim all EPO analogs. There may be other genetic sequence that code for EPO-Type products. Amgen has told how to make and use only a few of them and is therefore not entitled to claim all of them...[W]e do not intend to imply that genetic sequences cannot be valid where they are of a scope appropriate to the invention disclosed by an applicant. That is not the case here, where Amgen has claimed every possible analog of a gene containing about 4,000 nucleotides, with a disclosure of hot to make EPO and a very few analogs.

Finally, at page 1028, the CAFC concludes:

> Considering the structurally complexity of the EPO gene, the manifold possibilities for change in its structure, with an attendant uncertainty as to what utility will be possessed by these analogs, we consider that more is needed concerning identifying the various analogs that are within the scope of the claim, methods for making them, and structural requirements for producing compounds with EPO-like activity. It is not sufficient, having made the gene and a handful of analogs whose activity has not been clearly ascertained, to claim all possible genetic sequences that have EPO-like activity. Under the circumstances, we find no error in the court's conclusion that generic DNA sequence claims are invalid under section 112.

The rejection is maintained.

Claims 1-8, 11-14 and 16-20 are rejected under 35 U.S.C. 102(e) as being anticipated by Baker et al (WO 01/64888, published September 20, 2001 with priority to December 1, 2000) is maintained for reasons made of record in the Office Action mailed 7-2-04.

Applicants' arguments have been carefully considered but are not persuasive. Applicants argue that they are entitled to their earliest priority date of the provisional application and therefore the reference is not available because it is not prior to the filing date of the provisional application. This is not persuasive, priority is not granted to any of the prior Applicants because the claimed invention lacks utility, enablment and written description in the priority documents for reasons made of record.

Claims 1-8, 11-14 and 16-20 are rejected under 35 U.S.C. 102(e) as being anticipated by Baker et al (US PreGrant Publication published Feb 6, 2003 with an earlier filing date of September 20, 2000 with priority to December 1, 2000) is maintained for reasons made of record in the Office Action mailed 7-2-04.

Applicants' arguments have been carefully considered but are not persuasive. Applicants argue that they are entitled to their earliest priority date of the provisional application and therefore the reference is not available because it is not prior to the filing date of the provisional application. This is not persuasive, priority is not granted to any of the prior Applicants because the claimed invention lacks utility, enablment and written description in the priority documents for reasons made of record.

New Grounds of Rejection

The use of trademarks have been noted in this application. It should be capitalized wherever they appear and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner that might adversely affect their validity as trademarks.

The trademark American Type Culture Collection (ATCC ™) needs to be recognized wherever it appears.

Claims 1, 2, 3, 4, 5, 6, 13, 14 and 16-20 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification at pages 120-123 lacks complete deposit information for the deposit of the full length cDNA encoding the claimed polypeptide deposited at the American Type Culture Collection as set forth in embodiment (e) of claims 1, 2, 3, 4, 5, 6, 13, 14, 16 and dependent claims 17-20. The referral to the deposit on page 123 is an insufficient assurance that all required deposits have been made and all the conditions of 37 CFR 1.801-1.809 have been met. The specification states that pursuant to an

"agreement" between Genentech, Inc. and the ATCC™, permanent unrestricted availability to the public of the progeny of the culture upon issuance of "the pertinent US Patent" is provided for. This is insufficient because agreements are contracts that are revocable and the conditions therein are revocable. Further, it is unclear what would be considered the "pertinent US Patent". As such, Applicants are required to provide assurances that All restrictions upon pubic access to the ATCC™ accession number 203245 as specifically claimed, will be "irrevocably removed upon the grant of a patent from this application" specifically using this exact language. Since "agreements" are subject to revocation, this assurance is required for patent purposes. The assurances should be made by an affidavit or declaration by Applicants or Assignees or a statement by an attorney of record who has authority and control over conditions of the deposit over his or her signature and registration number. Applicants are specifically directed to MPEP 2424.01 that states "with one possible exception (37 CFR 1.808(b)), that all restrictions on the accessibility be irrevocably removed by the applicant upon the granting of the patent" are required see *Ex parte Hildebrand*, 15 USPQ2d 1662 (Bd. Pat. App. & Int. 1990.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-8, 11-14 and 16-20 are rejected under 35 U.S.C. 102(b) as being anticipated by Ashkenazi et al (WO 00/77037, published May 22, 2000).

Ashkenazi et al teach a nucleic acid encoding a polyeptide and a polypeptide lacking its signal peptide that is identical as compared with the polypeptide set forth in SEQ ID NO:52. SEQ ID NO:52 is identical as compared with SEQ ID NO:106 in Ashkenazi et al and encodes the PRO1411 polypeptide (see page 29, description for Figures 53 and 54). Ashkenazi et al contemplate fusion proteins including immunoglobulin fusion proteins with the PRO polypeptides (see pages 75-76). Ashkenazi et al contemplate portions of the PRO polypeptides (pages 71-72 (lines 12-15 in particular and page 76, lines 5-15).

Therefore, Ashkeanzi et al anticipate the instantly claimed invention. It is noted that a copy of this lenghty reference has not been provided herein because it has already been provided in related co-pending application 10/063,560.

Status of the Claims

All claims stand rejected.

Conclusion

This action is non-final in view of the new grounds of rejection and lines of argument set forth herein were not specifically set forth in the first office action on the merits.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patricia A. Duffy whose telephone number is 571-272-

0851. The examiner can normally be reached on M-Th 6:30 am - 6:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on 571-272-0864.

The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Patricia A. Duffy, Ph.D.

Primary Examiner

Art Unit 1645